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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/035,833	12/27/2001	Yusuke Nakamura	FORS-06904	2659

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EXAMINER	
SITTON, JEHANNE SOUAYA	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/035,833	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 6/28/2005.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,5-22,37-41,76 and 80-110 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,5-22,37-41,76 and 80-110 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1, 5-22, 37-41, 76, and 80-110 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are not sufficient to place in the instant application in condition for allowance. The following objections and rejections are either newly applied, as necessitated by amendment, or are reiterated. They represent the complete set being applied to the instant application. Response to arguments follows. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Acknowledgement is made as to the deletion of figure 313, starting at page 292 and ending at page 743 of the drawings filed 12/27/2001.

Priority

4. Acknowledgment is made of applicant's claim for foreign priority based on 5 applications filed in Japan on various dates between 12/27/2000 and 12/27/2001. Certified and translated copies of 4 applications (not the PCT) were submitted 6/28/2005. It is noted that the instantly claimed SEQ ID NOS do not appear in any of the priority documents. As such, the claims have been awarded the priority date of the instantly filed specification.

Specification

5. The disclosure is objected to because of the following:

A) The drawings contain sequences that are not identified by a sequence identifier. Chapter 2400 of the MPEP requires that all iterations of nucleic acid sequences of 10 or more nucleotides be designated by a proper sequence identifier. In response to the previous office action, applicants deleted claim 313, which appears to begin at page 292 of the drawings. However, the sheets of drawings still remain, interspersed in the remaining 291 sheets of drawings, which list sequences not identified by a sequence identifier. The objection is therefore maintained. It is noted that there were 743 pages of drawings filed 2/27/2001, however the "Brief Description of the Drawings" only referenced Figures 1-313. More pages of drawings exist which have not been identified by any figure legend or figure number. Such pages contain tables of information that cannot be discerned, as well as SNP information which have no explanation and are interspersed within pages the first 291 pages of drawing sheets. It is further noted, that due to the fact that no numbering system was proved for the 743 pages, they appear out of order, or in no particular order, and SNP information is interspersed with table information. Accordingly, their relevance to the instantly pending claims cannot be assessed.

B) Pages 2, 48, 105, 124, and 178 of the specification are missing. In their place, the specification contains duplicates of pages 157, 138, 191, 188, and 221, respectively. It is further noted, that the new application transmittal asserts that 263 pages of specification were submitted, but there are only 236 pages of specification for this application with the omissions and substitutions as set forth above. Additionally, it should be noted that no other omissions appear to be present other than the pages indicated, and that therefore the designation of the 263 pages appears to be an error.

In the reply filed 6/28/2005, applicants submit that records showed that these pages were not duplicated in the application as filed and request that the examiner disregard the duplicated sheets and enter the replacement sheets for missing pages 2, 48, 105, 124, and 178. This submission has been thoroughly reviewed but is insufficient to overcome the objection. The originally filed papers were re-reviewed and showed for example, to copies of page 157, one of which was in the place of page 2. the same is true for the other omissions listed above. Therefore, the pages supplied in the 6/28/2005 represent information that was not present in the application as filed, nor is there any evidence that such papers were contained in the originally filed specification. The submission is improper. Additionally, it should be noted that applicant's did not request that such papers be entered into the specification. However, should such amendment be filed, the amendment would be objected to under 112, first paragraph, New Matter.

C) There are only 743 pages of drawings, however the new application transmittal asserts that there are 745 pages. In response, applicants asserted that 746 pages were filed, however 746 pages could not be found. As noted in section A (B in the previous office action), the drawings are confusing because there does not appear to be a numbering system with respect to sheets within a figure. Additionally, even though Figure 313 was deleted, the remaining 291 pages contain tables and snp information with sequences, whose relevance to the remaining figures cannot be determined. The objection to the drawings is therefore maintained.

D) There are only 705 pages of sequence listing submitted with the application as filed. The sequence listing states that there are 4309 sequences. All appear to be present as the

sequence listing ends with SEQ ID NO: 4309, however the new application transmittal indicates that 1687 pages of sequence listing were filed, which indication appears to be in error.

Appropriate correction is required, however applicants should take care not to add new matter into the disclosure.

The examiner has reviewed the originally filed application papers, and found no evidence of the missing pages and sequence listing. Given the numerous discrepancies between what is contained in the application, and what was asserted to be filed, including the number of typographical errors with regard to the number of pages filed, and given that there is no evidence that the missing papers and sequences were present in the application papers originally filed, the objections are maintained.

New Matter

6. The sequence listing filed 10/30/2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: As stated above, only 705 pages of Sequence listing were filed with the specification. The sequence listing stated that 4309 sequences were contained in the sequence listing and all were present. However, on 10/30/2002, the sequence listing was changed such that it now contains 7669 sequences. This submission adds new matter to the specification. Although it appears that the 7669 sequences appear to refer to the 7669 sequences disclosed in table 1, as also noted previously, the specification is missing pages 105 and 124, which would be found in table 1. These pages were replaced with duplicates of pages 191 and 188 respectively, which do not provide for the missing sequences, namely SEQ ID

NOS: 3344-3360 or 4573-4642. Accordingly, it appears that the submission of 10/30/2002 has introduced new matter into the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

7. The response asserts that the originally filed papers contained the missing sequences. However, there is no evidence that such pages were present in the application as originally filed. Further, the examiner has reviewed the originally filed papers and did not find the missing pages. Further, a submission of a replacement pages would introduce new matter in the specification. The Objection is therefore maintained.

Claim Rejections - 35 USC § 101

8. Claims 1, 5-22, 37-41, 76, and 80-110 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility.

The claims are drawn to a method of identifying individuals with a polymorphism and to methods of screening subjects for genetic markers associated with drug metabolizing enzymes, by detecting the presence of at least one polymorphism in any one of SEQ ID NOS 7063, 7064, 7070, 7073, and 7074. Such methods are not supported by either a specific or substantial utility for the following reasons.

The specification asserts that determining DNA sequence variations in the human genome is useful for making accurate diagnoses, finding suitable therapies, and for understanding the relationship between genome variations and environmental factors in the

pathogenesis of diseases, the prevalence of conditions and the efficacy of therapies (page 1). The specification teaches that the invention identifies genetic polymorphisms relating to genes encoding enzymes associated with drug metabolism (page 3 and table 1). The specification teaches that these polymorphisms are either in coding regions and may affect function or activity of the enzyme, or in non coding regions which may alter the expression of the enzyme or the processing of an RNA transcript encoding the enzyme (page 3). However, such uses are general to any SNPs found in any drug metabolizing enzyme, and are not specific or substantial with regard to the instantly claimed SNPs. The specification does not teach which drug or treatment protocol would be affected by the instantly claimed polymorphisms, nor which diseases would be treated with regard to the presence or absence of such polymorphisms. While the claimed polymorphisms occur outside coding regions of CYP1B1, the specification does not teach or demonstrate whether such polymorphisms occur in 'regulatory' sequences of the gene, ie the promoter (for 5' flanking polymorphisms), or if they are in the gene at all. Additionally, the specification does not teach what the effect of such polymorphisms have on the activity, function, or expression of CYP1B1 RNA or enzyme, what, if any, effect such polymorphisms would have on a patient's response to therapy, or a patient's prognosis. At page 202, the specification shows an example of using SNP data in the thiopurine S-methyltransferase gene to correlate SNP genotypes and optimal amounts of a medicament for treatment validity and safety, however such enzyme provides no correlative information as to the usefulness of the SNP data for the CYP1B1 gene. While some polymorphisms would be expected to affect the activity, function or expression of the large number of genes genotyped in table 1, a large number would be expected to have no effect, especially when analyzed as a single polymorphism (that is no

haplotype analysis). However, the specification provides no information to determine which polymorphisms will have an effect. Further, even assuming that some polymorphisms would have an effect, the specification provides no information as to how to use the SNP information for CYP1B1 to use the effect in prescribing drug or treatment protocol for a subject or providing any prognosis. At pages 196-198, the specification teaches generally that the SNP information can be used to evaluate drugs and to indicate the safety and effectiveness of drugs and briefly teaches how some screening can be achieved, however the specification provides no information or assessment as to the effect, if any, of the polymorphisms for CYP1B1, let alone the claimed polymorphisms, nor how one of skill could use such information, for example in prescribing drug or treatment protocol for a subject or providing patient prognosis.

There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to

associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789). The unpredictability of the functionality or use of SNPs is not limited to diagnostic uses, but is found in drug response as well. Malhotra et al (Am. J. Of Psychiatry, vol. 161, pages 780-796, May 2004) teaches that while a T102C polymorphisms in the serotonin 5-HT2A gene was reported to have a significant association with the failure to respond to clozapine in 149 patients with chronic schizophrenia, such effect was not able to be replicated in a series of subsequent studies (see page 7829 col 2). Malhotra et al teach that definitive studies in larger group sizes, prospective clinical data, and comprehensive analysis of the gene will be needed to further address the role of this gene in antipsychotic drug response (see page 783, col. 1). In the instant case, the specification only provides information that the variant exists, but provides no guidance that it has any effect whatsoever on the CYP1B1 gene, expression, or activity, let alone any potential diagnostic or therapeutic effect.

The research contemplated by applicant(s) to characterize polymorphisms in drug metabolizing enzymes and to determine potential drug or therapeutic protocols, or patient prognosis, for unidentified diseases, does not constitute a specific and substantial utility. Identifying and studying the properties of a polymorphism itself or the mechanisms in which the polymorphism is involved does not define a "real world" context or use. Further experimentation would be required of the skilled artisan to determine a use for the claimed polymorphisms. However, in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), the court held that that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial

> utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to polymorphisms which have no identified activity or effect on the CYP1B1 enzyme. Until some actual and specific significance can be attributed to these polymorphisms, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention.

Response to Arguments

9. The response traverses the rejection. The response asserts that the application discloses and claims methods comprising detecting the recited polymorphisms associated with the CYP1B1 gene region and that as noted by Sundberg (referenced below and in the previous office action, page 13), CYP1B1 gene is responsible for about 75% of phase I dependent clinical trials. The response further asserts that Sundberg demonstrates the utility of detection methods that permit detection of particular allelic variations associated with the CYP1B1 gene. This argument as well as the teachings of Sundberg have been thoroughly reviewed but were found insufficient to overcome the rejection. Firstly, it is noted that Sundberg teaches that cytochromoe P450s as a group, not the CYP1B1 gene, is responsible for 75% of phase I dependent drug metabolism. Sundberg teaches that seven common CYP1B1 alleles have been identified but that the role of these allelic variants for the metabolism of oestradiol and polyaromatic hydrocarbons has been investigated with variable results (see page 99, para bridging cols 1 and 2). Sundberg further teaches that one might conclude from such data that none of these alleles would have any major importance with respect to altered function of CYP1B1 in vivo or in vitro. Secondly, as noted in

the previous office action and reiterated above, the specification provides no information or assessment as to the effect, if any, of the listed polymorphisms for CYP1B1, let alone the claimed polymorphisms, nor how one of skill could use such information, for example in prescribing drug or treatment protocol for a subject or providing patient prognosis. The specification does not teach which drug or treatment protocol would be affected by the instantly claimed polymorphisms, nor which diseases would be treated with regard to the presence or absence of such polymorphisms. While the claimed polymorphisms occur outside coding regions of CYP1B1, the specification does not teach or demonstrate whether such polymorphisms occur in 'regulatory' sequences of the gene, ie the promoter (for 5' flanking polymorphisms), or if they are in the gene at all. Additionally, the specification does not teach what the effect of such polymorphisms have on the activity, function, or expression of CYP1B1 RNA or enzyme, what, if any, effect such polymorphisms would have on a patient's response to therapy, or a patient's prognosis. Accordingly, one of skill in the art would not know what to do with the information that an individual did or did not possess a polymorphism at the claimed locations. The teachings of Sundberg do not remedy these deficiencies in the specification because Sundberg does not teach what the effect of these polymorphisms are nor what one of skill in the art would do with the information that an individual did or did not possess these specific polymorphisms. While the response asserts that because detection of variants of CYP1B1 genes has "such" established utilities, the methods of detection of these particular polymorphisms has utility, however the response does not state what the utility is, other than detection of themselves which is a circular argument. In effect, the response appears to assert that the polymorphisms have utility because one could detect them. This argument has been

thoroughly reviewed but was not found persuasive. As already discussed, neither the specification nor the art provide any activity or phenotypic effect for the instantly recited polymorphisms. Accordingly, other than detecting the polymorphisms to conduct further research to determine the use, if any, for the claimed polymorphisms, the research contemplated by applicant(s) to characterize the polymorphisms and to determine potential drug or therapeutic protocols, or patient prognosis, for unidentified diseases, does not constitute a specific and substantial utility. Identifying and studying the properties of a polymorphism itself or the mechanisms in which the polymorphism is involved does not define a "real world" context or use. Further experimentation would be required of the skilled artisan to determine a use for the claimed polymorphisms. Applicants arguments that "a skilled artisan would appreciate that the claimed methods for detection of particular variants can be used to detect these particular variants of the CYP1B1 gene in a subject or sample" does not constitute a specific or substantial utility because the specification does not disclose how one of skill in the art would use the information that an individual or sample does or does not possess one of the claimed polymorphism, other than to perform further research to characterize the polymorphism, which does not represent a patentable utility. As noted in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), the court held that that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to polymorphisms which have no identified activity or effect on the CYP1B1 enzyme. Until some actual and specific significance can be attributed to these polymorphisms, one of ordinary skill in the art would be required to perform additional experimentation in order to determine how to use the claimed invention. For these reasons and the reasons made of record above and in the previous office action, the rejection is maintained.

Claim Rejections - 35 USC § 112

10. Claims 1, 5-22, 37-41, 76, and 80-110 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

<u>The nature of the invention and the breadth of the claims:</u>

The claims are drawn to a method of identifying individuals with a polymorphism and to methods of screening subjects for genetic markers associated with drug metabolizing enzymes, by detecting the presence of at least one polymorphism in any one of SEQ ID NOS 7063, 7064, 7070, 7073, and 7074. However, the specification has not enabled on of skill in the art how to use the invention commensurate in scope with the claims.

The amount of direction or guidance:

The specification teaches that determining DNA sequence variations in the human genome is useful for making accurate diagnoses, finding suitable therapies, and for understanding the relationship between genome variations and environmental factors in the pathogenesis of diseases, the prevalence of conditions and the efficacy of therapies (page 1). The specification teaches that the invention identifies genetic polymorphisms relating to genes encoding enzymes associated with drug metabolism (page 3 and table 1). The specification teaches that these polymorphisms are either in coding regions and may affect function or activity of the enzyme, or in non coding regions which may alter the expression of the enzyme or the processing of an RNA transcript encoding the enzyme (page 3). At table 1, the specification teaches that the polymorphisms in SEQ ID NOS 7063, 7064, occur in the 5' flanking region of a nucleic acid sequence encoding the CYP1B1 (a cytochrome P450) enzyme and that the polymorphisms in SEQ ID NOS 7071, 7073, and 7074 occur 3' of exon 3 (page 160). None of these polymorphisms occur in a coding region of the nucleic acid. The specification teaches that an the "n" at position 21 of SEQ ID NOS 7073 and 7074 represents an "A" or a deletion at that position. SEQ ID NO: 7071 represents a deletion of a "T" at position 21 of SEQ ID NO: 7070.

SEQ ID NOS 7063 and 7064 possess a G/A or G/C polymorphism at position 21, respectively. It is noted that the specification does not teach the complete nucleic acid sequence encoding the CYP1B1 enzyme used for such analysis, therefore it is unclear as to which specific nucleotide in the gene such polymorphisms occur. Although, as stated previously, such polymorphisms occur outside coding regions, it is noted that it is unclear whether such polymorphisms occur in 'regulatory' sequences of the gene, ie the promoter (for 5' flanking polymorphisms), or if they are in the gene at all, but may be in genomic sequences flanking the CYP1B1 gene. Additionally, the specification does not teach what the effect of such polymorphisms has on the activity, function, or expression of CYP1B1 RNA or enzyme.

Presence and absence of working examples:

Apart from teaching that such polymorphisms were found by screening 48 unrelated people (page 199) the specification does not teach the effect, if any, that such polymorphisms might have on the activity, function, or expression of CYP1B1 RNA or enzyme. Further, the specification provides no working examples of any effect such polymorphisms would have on a patient's response to therapy, or a patient's prognosis, nor does the specification teach any examples of prescribing drug or treatment protocol, or establishing a patient's prognosis, based on whether or not someone had any of the claimed polymorphisms. At page 202, the specification shows an example of using SNP data in the thiopurine S-methyltransferase gene to correlate SNP genotypes and optimal amounts of a medicament for treatment validity and safety, however such enzyme provides absolutely no correlative information as to the usefulness of the SNP data for the CYP1B1 gene. While some polymorphisms would be expected to affect the

activity, function or expression of the large number of genes genotyped in table 1, a large number would be expected to have no effect, especially when analyzed as a single polymorphism (that is no haplotype analysis). However, the specification provides no information to determine which polymorphisms will have an effect. Further, even assuming that some polymorphisms would have an effect, the specification provides no information as to how to use the SNP information for CYP1B1 to use the effect in prescribing drug or treatment protocol for a subject or providing any prognosis. At pages 196-198, the specification teaches generally that the SNP information can be used to evaluate drugs and to indicate the safety and effectiveness of drugs and briefly teaches how some screening can be achieved, however the specification provides no information or assessment as to the effect, if any, of the polymorphisms for CYP1B1, let alone the claimed polymorphisms, nor how one of skill could use such information, for example in prescribing drug or treatment protocol for a subject or providing patient prognosis.

The state of the prior art and the predictability or unpredictability of the art:

Neither the pre nor the post filing date art provide any indication that any of the claimed polymorphisms have any effect on the activity or expression of the CYP1B1 enzyme, nor if or how the polymorphisms can be used to evaluate drug safety or effectiveness, nor how or if they can be used in prescribing drug or treatment protocol for a subject or providing patient prognosis. The claimed sequences, as noted previously, are in non-coding regions, however it is unclear if they are in the CYP1B1 gene at all. With regard to P450's, Sundberg teaches (Ingelman-Sundberg, M. hereinafter referred to as Sundberg; Naunyn-Schmiedeberg's Arch. Pharmacol. 2004; vol. 369, pages 89-104) teaches that the cytochrome P450s are responsible for about 75%

of phase I dependent drug metabolism as well as for the metabolism of a large amount of dietary constituents and endogenous chemicals (see abstract). With regard to CYP1B1, Sundberg teaches that it might have a role in the metabolism of oxidized growth-effector molecules (see page 99). Sundberg teaches that seven common CYP1B1 alleles have been identified but that the role of these allelic variants for the metabolism of oestradiol and polyaromatic hydrocarbons has been investigated with variable results (see page 99, para bridging cols 1 and 2). Sundberg further teaches that one might conclude from such data that none of these alleles would have any major importance with respect to altered function of CYP1B1 in vivo or in vitro. Downie (Downie et al; Current Pharmacogenetics, 2004, vol. 2, pages 243-254) teaches that specific inhibitors to CYP1B1 have been used to modulate the cytotoxic profile of a range of structurally diverse anti-cancer drugs with CYP1B1, but that despite the benefits of clinical inhibitors, further studies are required to establish whether CYP1B1 allelic variants would posses the same response as wild type CYP1B1 (see page 249, end of col 1-col 2). Therefore, while the post filing date art teaches of therapeutics with regard to CYP1B1, the art acknowledges that further studies are required to determine whether allelic variants of CYP1B1 would have the same response as wildtype. As already noted, neither the specification nor the art teach how or if the claimed polymorphisms have any effect on the expression or activity of CYP1B1. As these polymorphisms do not occur in any coding regions, nor is it clear if they occur in any regulatory region, one of skill in the art would not be able to predictably correlate any of the claimed polymorphisms with altered or maintained expression or activity of CYP1B1 to be able to use the polymorphism analysis let alone in prescribing drug or treatment protocol for a subject or providing patient prognosis as asserted by the specification.

There is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789). The unpredictability of the functionality or use of SNPs is not limited to diagnostic uses, but is found in drug response as well. Malhotra et al (Am. J. Of Psychiatry, vol. 161, pages 780-796, May 2004) teaches that while a T102C polymorphisms in the serotonin 5-HT2A gene was reported to have a significant association with the failure to respond to clozapine in 149 patients with chronic schizophrenia, such effect was not able to be replicated in a series of subsequent studies (see page 7829 col 2). Malhotra et al teach that definitive studies in larger group sizes, prospective clinical data, and comprehensive analysis of the gene will be needed to further address the role of this gene in antipsychotic drug response (see page 783, col. 1). In the instant case, the specification only provides information

that the variant exists, but provides no guidance that it has any effect whatsoever on the CYP1B1 gene, expression, or activity, let alone any potential diagnostic or therapeutic effect.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

In the instant case, a large quantity of experimentation would be required to determine a use for analysis which detected the claimed polymorphisms, and, as asserted by the specification, in prescribing a drug or treatment protocol based on the result of the detection assay and further providing a prognosis to the subject based on the presence or absence of the polymorphisms. While a large quantity of experimentation is not itself necessarily undue, in the instant case, given the lack of guidance in the specification as to what effect the claimed polymorphisms have on the expression or activity of CYP1B1, the lack of guidance in the art with regard to the possible effect of these polymorphisms, the teachings of unpredictability in the art with regard to CYP1B1 polymorphisms, the teachings in the art that further research is required to determine whether allelic variants of CYP1B1 have the same effect as wild type with regard to clinical inhibitors (drug response or treatment protocol), as well as the teachings in the art with regard to the unpredictability of the effect of polymorphisms in general, such analysis would be replete with unpredictable trial and error analysis. To practice the invention as it is claimed, the skilled artisan would have to determine the effect, if any, that such polymorphisms would have on the expression or activity of CYP1B1, and then to determine how to use such information. While the

level of skill in the art is high, based on the lack of guidance in the specification and the unpredictability taught in the art, the experimentation required of the skilled artisan is unpredictable and replete with an extremely large amount of trial and error analysis, requiring a large amount of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of working examples and the teachings of unpredictability in the art balanced *only* against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to make and use the methods of the claims.

Response to Arguments

11. The response traverses the rejection and asserts that the amended claims comprise methods of detecting the specified polymorphisms and that the specification provides guidance as to how to detect polymorphisms. These arguments have been thoroughly reviewed but were found unpersuasive for the reasons made of record in section 9 above. The instant rejection is based on rejection of the claims under 35 USC 101, as set forth above and in the previous office action. While the post filing date art teaches of therapeutics with regard to CYP1B1, the art acknowledges that further studies are required to determine whether allelic variants of CYP1B1 would have the same response as wildtype. As already noted, neither the specification nor the art teach how or if the claimed polymorphisms have any effect on the expression or activity of

CYP1B1. As these polymorphisms do not occur in any coding regions, nor is it clear if they occur in the CYP1B1 gene at all, one of skill in the art would not be able to predictably correlate any of the claimed polymorphisms with altered or maintained expression or activity of CYP1B1 to be able to use the polymorphism analysis in any meaningful way, let alone in prescribing drug or treatment protocol for a subject or providing patient prognosis as asserted by the specification. For these reasons and the reasons made of record above and in the previous office action, the rejection is maintained.

Claim Rejections - 35 USC § 102

12. Claims 1, 5, 12, and 37-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Han (Han et al WO 02/30951).

The claims are drawn to detecting a polymorphism in the sequences provided. The claims broadly encompass detecting the identity of a nucleotide at a specific position and therefore broadly encompass sequencing the CYP1B1 gene as a method of sequencing inherently determines the identity of a nucleotide at a specific position. Han teaches sequencing as well as the sequence of the CYP1B1 gene and surrounding region (See Fig. 1). Such nucleic acid comprises the claimed SEQ ID NOS. Han teaches providing nucleic acid from the subject and detecting the presence of at least one polymorphism (determining the nucleotide at every position of SEQ ID NOS 7070, 7073 and 7074). Therefore, Han anticipates the claimed invention.

Response to Arguments

13. The response traverses the rejection. The response asserts that Han does not teach detection of the specific polymorphisms as now present in the amended claim. This argument has been thoroughly reviewed but was found unpersuasive. While the claims have been amended to specify that certain positions can have different nucleotides present, in sequencing the CYP1B1 gene and surrounding region, which encompasses SEQ ID NOS 7070, 7073, and 7074, Han inherently teaches determining the identity of the nucleotide at each position, including the claimed polymorphic positions. The claims are not limited to detecting alleles at specific positions which are not included in the sequence of Han, but instead state that detection can comprise the presence or absence of specific nucleotides (7070: t or deletion; 7073: A or deletion; 7074: A or deletion) which are taught by Han. The claims are therefor not sufficient to distinguish the methods from that of Han just because Han does not identify the same positions as being polymorphic. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103

14. Claims 1, 12, 37, 39, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Accession number AC011074 (September 10, 2000).

The claims are drawn to detecting a polymorphism in the sequences provided. The claims broadly encompass detecting the identity of a nucleotide at a specific position and therefore broadly encompass sequencing the CYP1B1 gene as a method of sequencing inherently determines the identity of a nucleotide at a specific position. The claims broadly encompass sequencing the CYP1B1 gene and surrounding region which the Accession number teaches. Such nucleic acid comprises SEQ ID NO 7063, for example (see sequence alignment). Although

the accession number does not specifically teach providing a nucleic acid from a subject or a detection assay, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain nucleic acid from a subject as the accession number teaches that such DNA was sequenced from a homo sapiens genomic DNA sample.

Response to Arguments

15. The response traverses the rejections under 35 USC 103. The response asserts that the claims have been amended to recite specific polymorphisms. This argument has been thoroughly reviewed but was found unpersuasive. While the claims have been amended to specify that certain positions can have different nucleotides present, in sequencing the CYP1B1 gene and surrounding region, which the Accession number teaches, it is a property of such teaching of determining the identity of the nucleotide at each position, including the claimed polymorphic position. The claims are not limited to detecting alleles at specific positions which are not included in the sequence of the Accession number, but instead state that detection can comprise the presence different oligonucleotides (7063: G or A) which is taught by the Accession number. The claims are therefor not sufficient to distinguish the methods just because the Accession number does not identify the same positions as being polymorphic. Therefore, the rejection is maintained.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. No claims are allowable.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton
Primary Examiner
Art Unit 1634
9/15/05